



Research Article

In vitro and In silico evaluation of *Shunthi* (*Zingiber officinale* Roscoe.) to ascertain its role in Functional Dyspepsia

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Abstract

Introduction: Functional dyspepsia is a benign gastrointestinal disorder presenting with early satiety, post prandial fullness and discomfort in epigastrium. It is a multifactorial condition due to impaired gastric motility, visceral hypersensitivity and inflammation. Ayurveda classifies *Shunthi* (*Zingiber officinale* Roscoe.) under *Truptighna* group of medicinal plants. It is traditionally used for symptoms similar to FD. But the mechanism of action in functional gastrointestinal disorders is not yet understood. **Methodology:** *Z. officinale* rhizome ethanolic extract was assessed for total phenols (Folin-ciocalteu method), flavonoids (Aluminium chloride method) and Antioxidant assay (DPPH method) followed by network pharmacology and molecular docking approach to elucidate the multitargeted mechanism of *Shunthi* in FD. **Results:** *Z. officinale* rhizome showed phenolic content of 76.36 mg GAE/ gm of extract and flavonoid content of 6.55 mg QE/ gm of extract. The extract showed DPPH free radical inhibition activity with IC₅₀ 20.1 µg/mL. 285 phytoconstituents were retrieved from IMPPAT 2.0 and Dr. Duke's databases. ADME screening via SWISS-ADME was performed and 181 compounds were retained. Binding DB and Uniprot analyses helped to identify 57 bio-actives. Intersection with proteins associated with FD with Venny 2.1 revealed 34 common targets. A protein-protein interaction network was constructed using STRING database, followed by Gene Ontology and KEGG pathway enrichment analyses. The results identified serotonergic synapse, arachidonic acid metabolism, cancer related pathways and micro-RNA signalling pathways as the primarily modulated pathways. Topological analysis was done using Cytoscape. During molecular docking, it was understood that five key phytoconstituents namely dehydrogingerdione, 8-shagol, 10-shagol, gingerol and 8-gingerdione bind more effectively with stable binding scores (≥ -7 kcal/mol) to core targets PTGS2, TRPV1 and ALOX5. **Conclusion:** Modulation involving multiple targets and pathways indicates that *Shunthi* has the ability to act by regulation of inflammation and nociception, by maintaining gastrointestinal homeostasis. The study findings provide a rationale based on systems-pharmacology approach and form the basis for further experimental and clinical validation.

Keywords: *Shunthi*, *Zingiber officinale*, Functional Dyspepsia, *In vitro*, Network pharmacology, Molecular Docking

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Introduction

A balanced state of digestive power (*Agni*) is considered as one of the prime causes for Health as per Ayurveda. (1) This controls all metabolic processes in the body. Any impairment in its

functioning results in various diseases. (2) The present-day lifestyle with high protein and high fat food and sedentary habits has led to changes in the digestive pattern of the population leading to a number of digestive disorders. (3) Functional dyspepsia is one such condition.

Functional Dyspepsia (FD) is one of the most common gastrointestinal disorder which is benign in nature. It's presentation mimics other gastro intestinal pathologies and hence it is difficult to diagnose. FD is characterized by the presence of one or more symptoms such as early satiety, post prandial fullness, epigastric pain or burning and these symptoms are without any structural abnormalities as examined through imaging or endoscopy. These symptoms can be so severe that they interfere with the daily

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activities. In some cases, other symptoms like nausea, heartburn, vomiting can be seen but they are infrequent. (4) The condition affects more than 40% of the population worldwide. Global prevalence rates are 5-10 %. In Asia, this rate is around 5-30%. FD is found to be more common in women. This might be due to sex-specific differences in the functioning of the gastrointestinal tract. Differences also exist with respect to hormonal mechanisms, signalling of pain and maintenance of health. (5)

FD involves a complex pathophysiology and hence the exact mechanism of its manifestation is still not understood. The causes for FD are multi-fold including disturbance in gastric motility and altered gastric sensation or hypersensitivity. One of the many reasons can be inflammation in gastric and intestinal mucosa. In some cases, genetic predisposition or psychiatric comorbidity is also found. Further, the pathophysiology of FD is complex as several macroscopic and microscopic mechanisms are involved. The reason is determined to be eosinophilic degranulation and T cell recruitment, which results in moderate duodenal inflammation. Mitochondrial autophagy has been found to be the cause most recently. (6)

Shunthi (*Zingiber officinale* Roscoe.) is one of the popular medicinal plants most commonly used in treating digestive disorders. In Ayurveda it is mentioned in *Truptighna gana* (a group of 10 medicinal plants which act on satiety, *Trupti* means early satiety). The condition "*Trupti*" described in Ayurveda is characterized by symptoms which are similar to that of FD. *Z. officinale* is known for its several health benefits. The pharmacological functions of this medicinal plant, including as antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, cardiovascular, respiratory, anti-obesity, antidiabetic, antinausea, and antiemetic properties, have been demonstrated by a significant quantity of study. (7) Due to these actions *Z. officinale* can form a promising candidate in targeting Functional Dyspepsia. *Z. officinale* contains many complex phytoconstituents, the most important being phenolic compounds. Since FD is a multifactorial disease involving multiple pathological mechanisms, it is important to understand the mode of action of *Z. officinale* in FD. This understanding can be better established by the application of network pharmacology and molecular docking analysis of the drug by addressing specific targets of FD. This would offer scientific justification for the use of this herb in functional gastrointestinal disorder.

Materials and Methods

Procurement of drug and phytochemical analysis

The dried rhizome of *Z. officinale* were procured from KLE Ayurveda Pharmacy, Khasbag and was authenticated in Central Research Facility, AYUSH approved drug testing laboratory, KAHER's Shri B.M. Kankanawadi Ayurveda Mahavidyalaya, Shahapur, Belagavi. Preliminary organoleptic and physicochemical analyses were done followed by quantification studies.

The study sample was powdered and 5 gm powder was mixed with 100 mL Ethanol in a conical flask to prepare ethanolic extract by cold extraction method (agitation for 6 hours in flask shaker followed by maceration for 18 hours). The extract was then filtered and solvent was evaporated on water bath at low temperature below 50° C to prevent denaturation of phenolic compounds. This extract was used for further invitro analyses.

Total phenols content was determined by the Folin- Ciocalteu colorimetric method (8) with Gallic acid as standard. Calibration

curve was prepared with Gallic acid dissolved in methanol and diluted to 6.25 µg/ml - 100 µg/ml serial dilutions. Stock solution of sample extract (1mg/ml) was also prepared using ethanol as solvent. The sample extract and the standard solutions were taken in separate test tubes and added with 10 fold dilute Folin-Ciocalteu reagent along with 7.5 % sodium carbonate. The tubes were covered and allowed to stand for 30 minutes at room temperature and the absorbance was recorded at 760 nm in Shimadzu UV-1800 spectrophotometer. Blank containing methanol instead of sample/ standard was similarly analyzed. A calibration curve was prepared using Absorbance vs Concentration of gallic acid standard. The concentration of total phenols in the sample was determined by using a slope equation that was obtained from the standard graph. Results for total phenols were expressed as mg of gallic acid equivalent/gm dried extract.

Total flavonoid content was determined by Aluminium chloride colorimetric method (9) using quercetin as standard. Initially calibration curve was prepared with Quercetin dissolved in ethanol and diluted to 6.25µg/ml - 200 µg/ml serial dilutions. The test drug extract was dissolved in ethanol to prepare a stock solution with 1mg/ml concentration. The sample extract and quercetin in different dilutions were taken in separate test tubes and added with methanol, Aluminium Chloride 10%, Potassium Acetate 1M solution and distilled water to make the total volume 10 ml in each test tube and mixed well. A sample blank was prepared by replacing Aluminium chloride with distilled water. Sample and standard absorbance were measured with a Shimadzu UV-1800 spectrophotometer at a wavelength of 420 nm. A calibration curve using Absorbance vs Concentration of Quercetin standard was prepared, and the concentration of total flavonoid in the sample was determined by using a slope equation that was obtained from the standard graph. Results for total flavonoids were expressed as mg of quercetin equivalent/gm dried extract.

Further antioxidant activity was determined by DPPH method. (10) Ascorbic acid, plant extract, Methanol and DPPH chemical were used for analysis. Calibration curve of Ascorbic acid was prepared first by dissolving it in methanol and then diluting it to 6.25 µg/ml - 200 µg/ml of serial dilutions. Stock solution of extract (1 mg/ml) was prepared with methanol and further diluted to serial concentrations (6.25-200 µg/ml).

The serial concentrations of sample extract and standard Ascorbic acid were taken in test tubes and added with DPPH reagent dissolved in methanol making the final volume 5 mL and mixed well. Blank contained only DPPH dissolved in methanol.

The test tubes were then incubated in a dark room. Absorbance of Blank, Sample and Standard Solutions was measured with a Shimadzu UV-1800 spectrophotometer at a wavelength of 517 nm. Calibration curve was prepared using Absorbance vs Concentration of Ascorbic acid standard serial concentrations and the percentage (%) of radical scavenging activity in the sample was then determined using the slope equation.

Retrieval of bioactive phytoconstituents

The bioactive phytoconstituents of *Z. officinale* were retrieved from the databases IMPPAT 2.0 (Indian Medicinal Plants, Phytochemistry and Therapeutics), (11, 12) and Dr. Duke's Phytochemical and Ethnobotanical Database, (13) and a compiled final list of phytochemicals was prepared after removing the duplicates. The Pubchem database was used to obtain the structural information of the phytoconstituents (canonical smiles). Then SWISS ADME database was used to predict the ADME information of phytoconstituents in *Z. officinale*. (14) ADME was

assessed through parameters like GI absorption, Bioavailability and Lipinski violation. The phytoconstituents not fulfilling these criteria were removed.

Retrieval of targets associated with phytochemicals and disease targets

The specific protein targets of individual phytoconstituents were retrieved from Binding DB database, which identifies the targets based on structural similarity (85%). (15) The standard gene names of these targets were collected from Uniprot database. (16) The information about therapeutic targets of Functional Dyspepsia was obtained from gene cards database. (17) The term “Functional Dyspepsia” was used to search the targets related to FD. Then Venny 2.1.0 (18) tool was used to get the overlapping targets from *Z. officinale* and FD.

Construction of Protein-Protein Interaction (PPI) network

The common targets obtained from Venny 2.1.0 were then utilized to construct the Protein-Protein Interaction (PPI) network using STRING database version 11. (19) The species chosen was “Homo-sapiens” with 70 % similarity to confirm maximum accuracy and confidence level. This gave a PPI network diagram showing the interaction between the intersecting target genes.

KEGG pathway and Gene ontology (GO) enrichment analysis

The next step was to determine the functions of targeted genes and the signaling pathways involved. This was obtained from STRING database with statistical filter value fixed at 0.05 FDR cutoff. The top 10 interacting pathways and Gene ontology terms such as Biological processes, Molecular functions and Cellular component were obtained and were graphically presented.

Network construction

The common target genes, bio-active phytoconstituents and top pathways were added to Cytoscape 3.7.2 software. (20) Network construction was done between these three components. Topological assessment was done using network analyzer tool. Main therapeutic targets for FD and the most important phytochemicals were then determined based on the degree.

Molecular docking and visualization

The 3D crystal structures of core phytoconstituents were obtained from Pubchem database. Structures of important targets were procured from RSCB PDB (Protein Data Bank). (21) After downloading the target protein 3D structure, protein preparation was done using Biovia Discovery (22) software by removing the hetero atom, water and by adding the polar bonds to the chemical structure. Binding energies of core phytoconstituents to specific target proteins were predicted with the help of PyRx (23) software. Again, Biovia Discovery studio software was used to visualize the binding interactions with highest docking energy scores.

Results

The test sample was authenticated with the reference identification number CRF/Auth/93/2025-26. Primary organoleptic and Physicochemical analysis showed the following results: Organoleptic examination showed rhizome which was Buff coloured with agreeable and aromatic odour and agreeable pungent taste. Physicochemical analysis showed foreign matter % - Nil, Total Ash value (TA) 4.247 %, Acid insoluble ash (AIA) 0.772 %, Water soluble extractive (WSE) 15.785 % and Alcohol soluble extractive (ASE) 6.125 %.

Total phenolic content found in the test sample was 76.36 +/- 0.29 mg GAE/ gm of extract. Total flavonoid content was 6.55 +/- 1.12 mg QE/ gm of extract.

The antioxidant activity analysed by DPPH method showed an IC₅₀ value of 20.1 µg/mL. The results of inhibition of free radical are shown in the table 1.

Table 1: Depicting the percentage inhibition of free radical by DPPH method

Concentration of extract (µg/ mL)	Mean inhibition percentage of free radical
15.625	48.5687
31.25	53.5305
62.5	59.1125
125	68.3683
250	78.7213
500	86.3549

Retrieval of bioactive phytoconstituents

Bioactive phytoconstituents of *Z. officinale* were collected from IMPPAT and Dr. Duke's databases and also from published literature by using the botanical name as the search term. The search revealed 285 phytoconstituents. After screening for ADME and removing those having low GI absorption, bioavailability less than 0.55 and Lipinski violation greater than 1, the list narrowed down to 181 active phytochemicals.

Retrieval of targets associated with phytochemicals of *Z. officinale* and disease targets for Functional Dyspepsia

Among the 181 active phytoconstituents, 57 showed probable protein targets when screened through Binding DB. As per the prediction, these compounds can target 66 unique genes. A total of 3491 disease targets related to FD were obtained from Gene Cards database by using “Functional Dyspepsia” as the search term. These along with 66 unique targets of *Z. officinale* phytoconstituents were intersected using Venny 2.1.0 to obtain the common targets. It was found that there are 34 common targets for *Z. officinale* in the possible treatment of Functional Dyspepsia (Figure 1a). Out of 57 active phytochemicals showing targets, 43 phytochemicals were found to interact with 34 common targets identified by Venny 2.1.0.

Gene ontology (GO) enrichment and KEGG pathway analysis

The protein-protein interaction network was then obtained by inserting the 34 intersecting gene targets into the STRING database (Figure 1b). Three components—Molecular Function (MF), Cellular Component (CC), and Biological Process (BP)—were used to further investigate gene ontology (GO) enrichment. The top ten GO keywords for each ontology component are shown in Figures 1c, 1d and 1e. The results showed that BP reacted to unsaturated fatty acid metabolic process, icosanoid metabolic process and arachidonic acid metabolic process. CC responded to nuclear envelope lumen and perinuclear cytoplasm. MF reacted to monooxygenase activity, NFκB binding, Heme binding, and oxidoreductase activity operating on paired donors with incorporation or reduction of molecular oxygen.

The KEGG pathways enrichment data revealed that the pathways which are primarily modulated are serotonergic synapse, arachidonic acid metabolism, chronic myeloid leukemia, pathways in cancer and microRNAs in cancer (Figure 2).

Figure 1a: Venn diagram showing the intersecting targets of *Shunthi* (*Z. officinale*) and Functional Dyspepsia, **Fig 1b:** Protein protein interaction network obtained by STRING database, **Fig 1c, 1d and 1e:** Bubble plot diagram depicting the top 10 annotations for three sections of Gene Ontology analysis namely Molecular function, Cellular component and Biological processes.

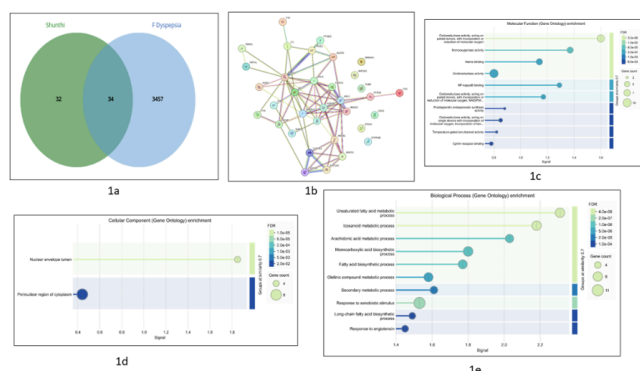
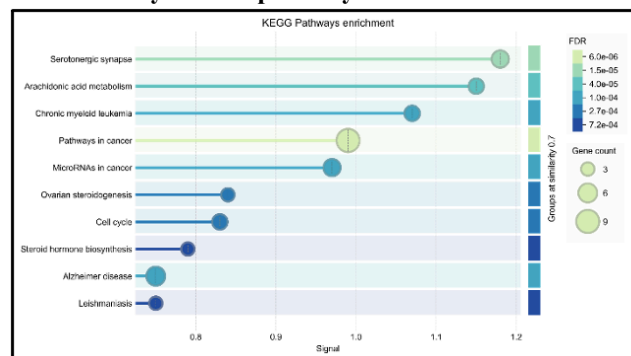


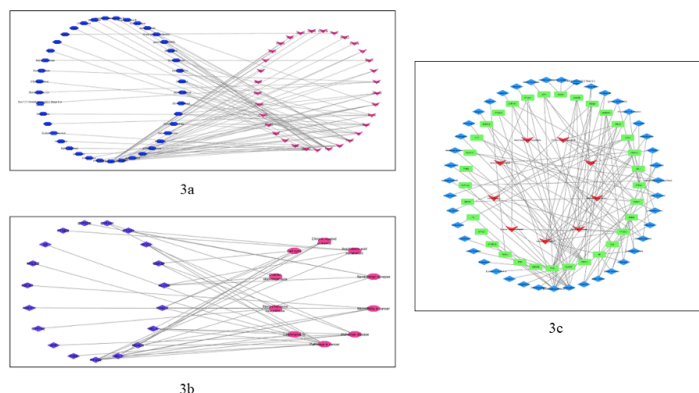
Figure 2: Bubble plot diagram for top 10 pathways obtained by KEGG pathway enhancement



Network construction and topological analysis

34 FD intersecting gene targets and 43 bioactive phytochemicals were exported to Cytoscape 3.7.2 software. The “Compound-Target” network contained 74 nodes and 176 edges (Figure 3a). Five core compounds Dehydrogingerdione, 8 Shagol, 10 Shagol, Gingerol and 8 gingerdione were filtered out in degree value after analysis using Network analyse tool in Cytoscape 3.7.2 software. The primary targets identified were TRPV1, ALOX5 and PTGS2.

Figure 3a: Showing the compound – target network of *Shunthi* (*Z. officinale*), **Fig 3b:** Showing the target – pathway network of *Shunthi* (*Z. officinale*) in FD, **Fig 3c:** Showing the merged network of compound - target - pathway of *Shunthi* (*Z. officinale*) in FD



The top 10 signaling pathways with significant p-value and associated targets were exported to Cytoscape 3.7.2 software to construct “Target-Pathway” network (Figure 3b). Top 4 pathways were determined using the network analyzer tool. PTGS2, HDAC1, HDAC2, ABL1 and RELA were identified as the most interacted targets of Target-Pathway network. In order to understand the molecular basis for understanding the mode of action of *Z. officinale* in FD, the interrelationships between phytochemicals, targets and pathway interactions were developed into a network. The network thus obtained provided a basic understanding of mode of action of *Z. officinale* active phytochemicals in FD.

Prediction of binding energies of core phytochemicals to specific target proteins

The core phytoconstituents and the most interacting targets were docked to determine the binding energies (Table 2). As per the previous literature, interactions between ligand and receptor protein are more stable when the binding energies are equal to or less than -7 Kcal mol⁻¹. All five core compounds Dehydrogingerdione, 8 Shagol, 10 Shagol, 6 Gingerol and 8 Gingerdione showed strong docking energies with the core targets TRPV1, ALOX5 and PTGS2. The standards drug Omeprazole was docked against the same targets and the binding energies were noted and compared with that of core phytoconstituents in *Z. officinale*. After molecular docking, the compounds with strongest docking scores were visualized with the help of BIOVIA Discovery studio. 3D–2D pictures of the binding poses of these along with the interacting amino acids are shown in the figure 8.

Table 2: Binding energies of compounds and core genes

Ligand name	Core Gene PDB ID	Binding energy (Kcal mol ⁻¹)
10 Shagol	TRPV1 (8gfa)	-7.2
8 Gingerdione	TRPV1 (8gfa)	-6.9
6 Gingerol	TRPV1 (8gfa)	-6.8
Omeprazole	TRPV1 (8gfa)	-6.6
Dehydrogingerdione	PTGS2 (5F1A)	-8
8 Shagol	PTGS2 (5F1A)	-7.6
8 Gingerdione	PTGS2 (5F1A)	-6.9
Omeprazole	PTGS2 (5F1A)	-8.7
8 Shagol	ALOX5 (3v99)	-7.2
Dehydrogingerdione	ALOX5 (3v99)	-6.2
Omeprazole	ALOX5 (3v99)	-8

Figure 4: Docking poses of 10 Shagol and standard Omeprazole with target TRPV1 with most stable binding energies

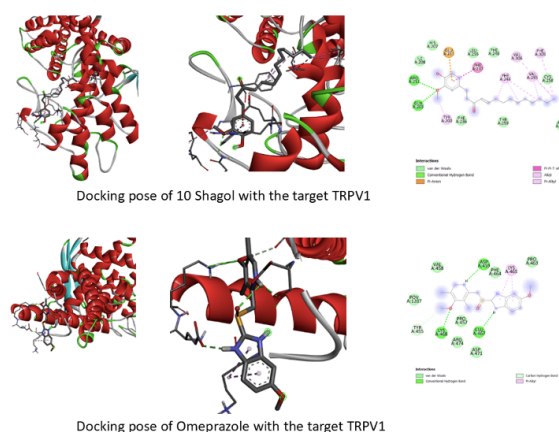
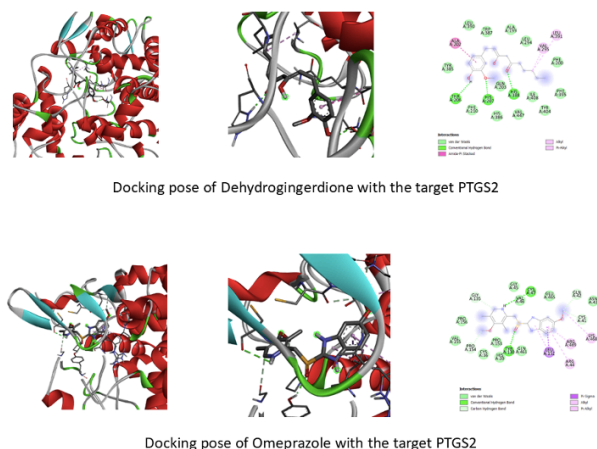


Figure 5: Docking poses of Dehydrogingerdione and standard Omeprazole with target PTGS2 with most stable binding energies



Discussion

Z. officinale is a commonly used herb in culinary practices. It has found vast application in clinical practice especially in treating disorders of gastro intestinal system.

In the present study, phenols was found to be 76.36 +/- 0.29 mg GAE/ gm of extract and flavonoids were quantified as 6.55 +/- 1.12 mg QE/ gm of extract in the drug along with its antioxidant activity analysed by DPPH method showing an IC₅₀ value of 20.1 µg/mL. From earlier evidences it is known that Polyphenols influence intestinal barrier integrity, immune responses, signaling pathways and gut microbiota, contributing to maintenance of gastrointestinal health. (24) Further antioxidant activity found in the test drug supports its action in immune mediated GI disorders like FGIDs (Functional Gastro intestinal disorders).

Application of network pharmacology and molecular docking analysis was done to understand the mode of action of *Z. officinale* in Functional Dyspepsia. FD is a multifactorial disease involving complex pathology mainly predominated by inflammatory and immune mediated changes along with the most recently identified cause, mitochondrial autophagy.

In the present study, five core compounds in *Z. officinale* namely Dehydrogingerdione, 8 Shagol, 10 Shagol, 6 Gingerol and 8 Gingerdione were identified during network analysis for their possible action in FD. Omeprazole, a drug belonging to Proton pump inhibitor group which is a part of standard drug regimen for FD was used as a comparator. 10 Shagol showed the most stable binding energy (-7.2) for the target TRPV1 which is better than that of standard drug omeprazole (-6.6). Dehydrogingerdione showed most stable energy (-8) for the target PTGS2 which is close to the binding energy of Omeprazole (-8.7). 8 Shagol showed most stable energy (-7.2) for the target ALOX5 while that of Omeprazole was -8.

Previous study shows that Dehydrogingerdione has the ability to attenuate nitric oxide synthase (iNOS, NOS2), cyclooxygenase-2 (COX-2), interleukin-1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α) and inhibit nuclear factor-κB translocation to the nucleus. It also downregulates the expression of IL-1β, IL-6, and IL-10 genes. (25) It has been proven to trigger apoptotic cell death through mitochondrial pathway. (26) It also inhibits lipid peroxidation and acts as free radical scavenger.

An earlier in-vivo study on dextran sodium sulfate-induced colitis mouse model showed that 6-, 8-, and 10-shagol can effectively inhibit inflammation through regulation of NF-κB signaling pathway. 10-shagol was shown to possess the most effective anti-inflammatory activity. (27) In the present study, anti-inflammatory activity of *Z. officinale* was confirmed by DPPH assay.

Gingerol is less pungent aromatic active phytochemical present in dry ginger. It is closely related to piperine and capsaicine. In a previous study, it showed anti-inflammatory response by inhibition of prostaglandin and leukotriene biosynthesis and suppression of 5-lipoxygenase. (28) Further different analogues of Gingerol such as 6-, 8- and 10- Gingerol have been proven for their antioxidant potential against DPPH radical, superoxide radical and hydroxyl radical. (29) Gingerol also has potent anti-inflammatory activity. This action takes place via inhibition of pro-inflammatory cytokines and presentation of antigen by LPS-mediated macrophages. The compound is shown to inhibit LPS-induced NOS and COX-2 in murine cell lines. (30)

8 gingerdione hasn't been particularly studied in detail for its pharmacological actions. Closely related structural analogues like 1-dehydro- [10] - gingerdione have shown potent inhibition of IKKβ/NF-κB pathway, resulting in the suppression of inflammatory genes in macrophages. (31)

During network pharmacology analysis, it was seen that *Z. officinale* phytochemicals show most stable binding energies with three important targets related to FD namely PTGS2, TRPV1 and ALOX5.

PTGS2 codes for Prostaglandin G/H synthase 2 and is also called cyclooxygenase. It catalyzes the first two steps in the arachidonic acid metabolism. This is the key enzyme involved in the biosynthesis of prostaglandin (PG)₂ and H₂. It is regulated by specific stimuli resulting in the biosynthesis of prostaglandin which in turn is responsible for inflammation and mitogenesis. (32) A previous study demonstrated that PTGS2, the gene which encodes COX2, is closely related to the enriched signaling pathways of pathogenic inflammatory response and immune cells infiltration. (33) The ability of PTGS2 in modulating the inflammation has led to the development of COX2 inhibitors as anti-inflammatory agents. According to earlier research, PTGS2 can alter the capacity of gastrointestinal tract to withstand and react to damage. Additionally, it has been discovered that COX 2 mediates crucial elements of mucosal defence, thereby considerably helps to mitigate irritation in the gastrointestinal tract. Additionally, it controls ulcer healing and has a role in long-term alterations in GI processes following recurrent inflammation. (34) This indicates that the inhibition of this target by *Z. officinale* might play a major role in controlling the inflammatory changes in FD.

TRPV1 (transient receptor potential vanilloid 1) channel is present on nociceptive terminal. It acts as a molecular transducer to depolarize the second order neurons in the spinal cord. They are then transmitted to specific brain areas of higher order, resulting in the sensation of pain. Thus, TRPV1 triggers pain pathway. TRPV1 is the only receptor of this family which is activated by Capsaicin (found in chilli/ pepper and responsible for pungent taste). Inhibition of TRPV1 can have therapeutic values in treating pain. (35) A previous study found that patients with functional dyspepsia showed higher levels of expression of TRPV1, indicating its role in the pathogenesis of FD. (36) There are evidences to suggest that TRPV1 causes exaggerated visceral sensitivity in FD. But desensitization of this target may lead to reduction in FD symptoms as evidenced by prolonged treatment

with Capsaicin. This effect may be because the receptor TRPV1 becomes refractory to nociceptive and mechanical stimuli on long term exposure to the irritant capsaicin. (37) Similar action might be seen in case of *Z. officinale* on chronic gastrointestinal symptoms, which is found to act through modulation of TRPV1.

ALOX5 encodes a gene of lipooxygenase family. It plays a major role in the synthesis of proinflammatory mediator leukotrienes by catalysing the peroxidation of arachidonic acid. This gene has a major role to play in mediating inflammatory process and lipid peroxidation and also cell death by apoptosis, ferroptosis, and pyroptosis. (38) There are no studies so far linking this gene directly to Functional dyspepsia. But since inflammatory response is involved in the disease pathogenesis of FD, ALOX5 can be considered as a potential target to modulate the disease process. The bioactive phytoconstituents of *Z. officinale* may function in FD by regulating the phosphorylation of ALOX5.

Conclusion

FD is a functional disorder characterised by multiple pathological changes. *Shunthi* is the most common drug used for treating many disorders related to the gastrointestinal tract including FD. The present study tried to relate the action of *Shunthi* phytocompounds to specific targets of Functional Dyspepsia by invitro and insilico assays. The study showed that phenols and flavonoids present in the trial drug have a major role in addressing the pathological changes in FD via anti-inflammatory and anti-oxidant mechanisms. *Shunthi* might act by modulation of serotonergic synapse, arachidonic acid metabolism, pathways in cancer and microRNAs in cancer. It acts on key targets like PTGS2, TRPV1 and ALOX5 through bioactives like Dehydrogingerdione, 8 Shagol, 10 Shagol, Gingerol and 8 Gingerdione. The study also showed that these five bioactives present in *Shunthi* showed good interaction with the active sites of core targets PTGS2, TRPV1 and ALOX5 exhibiting good docking scores ($>/=-7$).

Thus, *Shunthi* can potentially treat FD by addressing the multiple pathological mechanisms involved. GC-MS / LC-MS analysis of *Shunthi* can help in identifying the specific compounds responsible for the said action which was not done in the present study. Further invivo and clinical studies can be conducted to validate the actions. *Shunthi* can be a promising drug to address functional gastrointestinal disorders where currently available drug treatment has got its limitations.

Author Contributions

The author contributions for this research are as follows: “Conceptualization: DK and AC; Data collection and literature search: DK; Writing – original draft: DK; Reviewing & Editing: DK and AC; Approval of final manuscript: DK and AC.

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Conflicts of Interest: The authors declare no conflict of interest.

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